

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|---|---|
| (51) International Patent Classification 5: C07D 409/12, A61K 31/33, C07D 213/75, 417/12, 401/12, 403/12, 413/12 | | A1 | (11) International Publication Number: WO 94/14801 |
| | | | (43) International Publication Date: 7 July 1994 (07.07.94) |
| (21) International Application Number: PCT/EP93/03666 | | (81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). | |
| (22) International Filing Date: 21 December 1993 (21.12.93) | | Published <i>With international search report.</i> | |
| (30) Priority Data: 9227048.7 29 December 1992 (29.12.92) GB 9304414.7 4 March 1993 (04.03.93) GB 9306459.0 29 March 1993 (29.03.93) GB | | | |
| (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Boreford, Middlesex 9EP TW8 (GB). | | | |
| (72) Inventors; and (75) Inventors/Applicants (for US only): FORBES, Ian, Thomson [GB/GB]; SmithKline Beecham Pharmaceuticals, Colindale Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). MARTIN, Roger, Thomas [GB/GB]; SmithKline Beecham Pharmaceuticals, Colindale Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). JONES, Graham, Elgin [GB/GB]; SmithKline Beecham Pharmaceuticals, Colindale Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). | | | |
| (74) Agent: GIDDINGS, Peter, J.; SmithKline Beecham, Intellectual Property, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB). | | | |
| (54) Title: HETEROCYCLIC UREA DERIVATIVES AS 5HT_{2C} AND 5HT_{2B} ANTAGONISTS | | | |
| <p style="text-align: center;">(I)</p> | | | |
| (57) Abstract | | | |
| <p>A compound of formula (I) or a salt thereof wherein: P is a quinoline, isoquinoline, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur; J is a ring system selected from quinoline, tetrahydroquinoline, indole, indazole, benzothiophene, indene, indane, benzothiazole or benzofuran; R¹ is hydrogen, C₁-alkyl, halogen, NR⁵R⁶ or OR⁷, where R⁵, R⁶ and R⁷ are independently hydrogen or C₁-alkyl; and R² and R³ are independently hydrogen or C₁-alkyl. R⁴ is C₁-alkyl, OR⁸ or halogen, where R⁸ is hydrogen or C₁-alkyl; and n is 1 or 2; provided that when P is other than pyridyl, J is not indoline, P and J are not both 6-methoxy quinoline, 8-hydroxy quinoline or 2-methyl quinoline, when J is quinoline or 2-methyl quinoline, P is not 2-thiazolyl, when P and J are both quinoline and R¹, R² and R³ are all hydrogen, R⁴ is not hydrogen or 6-methoxy. Compound of formula (I) and their pharmaceutically acceptable salts have 5HT_{2C} receptor antagonist activity and are believed to be of potential use in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse, schizophrenia and/or disorders associated with spinal trauma and/or head injuries.</p> | | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|--|----|--------------------------|
| AT | Austria | GB | United Kingdom | MR | Maritania |
| AU | Australia | GE | Georgia | MW | Malawi |
| BB | Barbados | GN | Guinea | NE | Niger |
| BE | Belgium | GR | Greece | NL | Netherlands |
| BF | Burkina Faso | HU | Hungary | NO | Norway |
| BG | Bulgaria | IE | Ireland | NZ | New Zealand |
| BJ | Benin | IT | Italy | PL | Poland |
| BR | Brazil | JP | Japan | PT | Portugal |
| BY | Belarus | KE | Kenya | RO | Romania |
| CA | Canada | KG | Kyrgyzstan | RU | Russia Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | KR | Republic of Korea | SE | Sweden |
| CH | Switzerland | KZ | Kazakhstan | SI | Slovenia |
| CI | Côte d'Ivoire | L1 | Liechtenstein | SK | Slovakia |
| CM | Cameroon | LK | Sri Lanka | SN | Senegal |
| CN | China | LU | Luxembourg | TD | Chad |
| CS | Czechoslovakia | LV | Latvia | TG | Togo |
| CZ | Czech Republic | MC | Monaco | TJ | Tajikistan |
| DE | Germany | MD | Republic of Moldova | TT | Trinidad and Tobago |
| DK | Denmark | MG | Madagascar | UA | Ukraine |
| ES | Spain | ML | Mali | US | United States of America |
| FI | Finland | MN | Mongolia | UZ | Uzbekistan |
| FR | France | | | VN | Viet Nam |
| GA | Gabon | | | | |

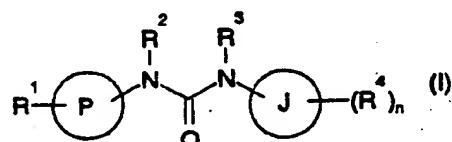
HETEROCYCLIC UREA DERIVATIVES AS 5HT2C AND 5HT2B ANTAGONISTS

This invention relates to compounds having pharmacological activity, to a process for their preparation, to compositions containing them and to their use in the treatment of mammals.

WO 92/05170 describes certain urea derivatives which are described as possessing 5HT_{1C} receptor antagonist activity. Quinolyl urea derivatives are also disclosed in J. Med. Chem., 1992, 35, 252, J. Het. Chem., 1968, 5, 371 and DE 2847792. The 5HT_{1C} receptor has recently been reclassified as the 5HT_{2C} receptor [P. Hartig et al., Trends in Pharmacological Sciences (TIPS) 1993].

A structurally distinct class of compounds has now been discovered, which have been found to have 5HT_{2C} receptor antagonist activity. Certain compounds of the invention also show 5HT_{2B} receptor antagonist activity, the 5HT_{2B} receptor being previously known as the fundus receptor [P. Hartig et al., Trends in Pharmacological Sciences (TIPS) 1993]. 5HT_{2C}/5HT_{2B} receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimers disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

In a first aspect the present invention therefore provides a compound of formula (I) or a salt thereof:



25

wherein:

P is a quinoline, isoquinoline, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

30 J is a ring system selected from quinoline, tetrahydroquinoline, indoline, indazole, benzothiophene, indene, indane, benzothiazole or benzofuran;

R¹ is hydrogen, C₁₋₆ alkyl, halogen, NR⁵R⁶ or OR⁷, where R⁵, R⁶ and R⁷ are independently hydrogen or C₁₋₆ alkyl; and

R² and R³ are independently hydrogen or C₁₋₆ alkyl.

35 R⁴ is C₁₋₆ alkyl, OR⁸ or halogen, where R⁸ is hydrogen or C₁₋₆ alkyl; and

n is 1 or 2;

provided that

- when P is other than pyridyl, J is not indoline,
- P and J are not both 6-methoxy quinoline, 8-hydroxy quinoline or 2-methyl quinoline,
- 5 • when J is quinoline or 2-methyl quinoline P is not 2-thiazolyl,
- when P and J are both quinoline and R¹, R² and R³ are all hydrogen, R⁴ is not hydrogen or 6-methoxy.

C₁-6alkyl groups, whether alone or as part of another group, can be straight chain or branched.

10 The urea moiety can be attached to a carbon or, when present, a suitable nitrogen atom of the ring P, preferably it is attached to a carbon atom. The urea moiety can be attached to any suitable carbon atom of the aromatic 6-membered ring of the ring J.

Suitable moieties when the ring P is a 5-membered aromatic heterocyclic ring include isothiazolyl, isoxazolyl, thiadiazolyl and triazolyl. Suitable moieties when the ring P is a 6-membered aromatic heterocyclic ring include, for example, pyridyl, pyrimidyl or 15 pyrazinyl. When P is a quinoline or isoquinoline residue, the urea moiety can be attached at any position of the ring, preferably to the 4-position.

The ring J can be quinoline, tetrahydroquinoline, indoline, indazole, benzothiophene, indene, indane, benzothiazole or benzofuran. Preferably J is 3- or 6-quinoline, 5-indoline, 20 5-benzothiophene, 5-indene, 5-indane, 5-indazole or 5-benzofuran. Most preferably J is 5-benzothiophene.

The rings P and J can be substituted at any suitable position.

Preferably P is 3-pyridyl.

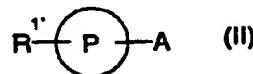
Preferably R¹, R² and R³ are all hydrogen.

25 R⁴ groups can be attached to any suitable carbon atom of the ring J or, when R⁴ is C₁-6alkyl, to a nitrogen atom if present. When n is 2, the resulting R⁴ groups can be the same or different.

Preferred compounds of formula (I) include:

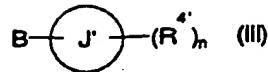
- N-5-(Benz[b]thienyl)-N'-(3-pyridyl)urea
- 30 N-(5-Indenyl)-N'-(3-pyridyl) urea
- N-(1,1-Dimethyl-5-indenyl)-N'-(3-pyridyl) urea
- N-(5-Benzothiazolyl)-N'-(3-pyridyl) urea
- N-(5-Benzofuryl)-N'-(3-pyridyl) urea
- N-(1-Methyl-5-indolinyl)-N'-(3-pyridyl)urea
- 35 N-(3-Pyridyl)-N'-(3-quinolinyl) urea
- N-(3-Pyridyl)-N'-(6-quinolinyl) urea
- N-(2-Methyl-4-quinolinyl)-N'-(3-pyridyl) urea
- N-5-(Benz[b]thienyl)-N'-(2-methyl-4-quinolyl) urea

- N-(3-Pyridyl)-N'-(5-quinolinyl) urea
- N-(3-Pyridyl)-N'-(8-quinolinyl) urea
- N-(5-Indanyl)-N'-(3-pyridyl) urea
- N-(3-Pyridyl)-N'-(6-(1-methyl-1,2,3,4-tetrahydro)quinolinyl)urea
- 5 N-(1-methyl-5-indazolyl)-N'-(3-pyridyl)urea
- N-(3-Methyl-5-benzo[b]thienyl)-N'-(3-pyridyl)urea
- N-(2-Methyl-5-benzo[b]thienyl)-N'-(3-pyridyl)urea
- N-(4-Methyl-5-benzo[b]thienyl)-N'-(3-pyridyl)urea
- N-(5-Benzo[b]thienyl)-N'-(3-methyl-5-isoxazolyl)urea
- 10 N-(5-Benzo[b]thienyl)-N'-(3-methyl-5-isothiazolyl)urea
and pharmaceutically acceptable salts thereof.
- 15 The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.
- 15 Compounds of formula (I) may form solvates such as hydrates, and the invention also extends to these forms. Certain compounds of formula (I) may also form N-oxides or S-oxides. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.
- 20 Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. Certain compounds of formula (I), for example those where R^2 and/or R^3 are hydrogen, may exist tautomERICALLY in more than one form.
- 25 The invention extends to these and any other tautomeric forms and mixtures thereof.
- In a further aspect, the present invention provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:
- 30 the coupling of a compound of formula (II);



with a compound of formula (III);

35



wherein P and n are as defined in relation to formula (I), A and B contain the appropriate functional group(s) necessary to form the moiety, $-\text{NR}^2'\text{CONR}^3'$ when coupled, the 5 variables R^1 , R^2 , R^3 and J' are R^1 , R^2 , R^3 , and J respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any R^1 , R^2 , R^3 and J' , when other than R^1 , R^2 , R^3 and J respectively to R^1 , R^2 , R^3 and J , interconverting R^1 , R^2 , R^3 and J and forming a pharmaceutically acceptable salt thereof.

10 Suitable examples of groups A and B include:

- (i) A is $-\text{N}=\text{C}=\text{O}$ and B is $-\text{NHR}^3'$,
- (ii) A is $-\text{NR}^2'\text{COL}$ and B is $-\text{NHR}^3'$,
- (iii) A is $-\text{NHR}^2'$ and B is $\text{NR}^3'\text{COL}$,
- 15 (iv) A is NHR^2' and B is $-\text{N}=\text{C}=\text{O}$ or
- (v) A is halogen and B is $-\text{NR}^3'\text{CONHR}^2'$

wherein R^2' and R^3' are as defined above and L is a leaving group. Examples of suitable leaving groups L include halogen such as chloro, bromo, imidazole or phenoxy or phenylthio optionally substituted for example with halogen.

20 When A is $-\text{N}=\text{C}=\text{O}$ and B is NHR^3' or when A is NHR^2' and B is $-\text{N}=\text{C}=\text{O}$ the reaction is suitably carried out in an inert solvent for example dichloromethane or toluene at ambient temperature.

25 When A is $-\text{NR}^2'\text{COL}$ and B is NHR^3' or when A is $-\text{NHR}^2'$ and B is $-\text{NR}^3'\text{COL}$, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

30 When A is halogen and B is $-\text{NR}^3'\text{CONHR}^2'$, the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of a base.

35 Interconversions of compounds of formula (I) to further compounds of formula (I) can be carried out using standard procedures. Suitable examples of groups R^1 and R^4 which are convertible to R^1 and R^4 alkyl groups respectively, include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed by hydrogenolysis in an inert solvent. Hydrogen substituents may be obtained from alkoxy carbonyl groups which may be converted to hydrogen by hydrolysis and

decarboxylation. When R^4 is hydroxy it is preferably protected in the compound of formula (II) as, for example, benzyl which is removed by hydrogenation.

When R^2 is C_{1-6} alkyl and R^3 is hydrogen it is possible to introduce a C_{1-6} alkyl group at the R^3 position by conventional alkylation using 1 molar equivalent of a C_{1-6} alkyl halide and 1 molar equivalent of a suitable base in an inert solvent. Suitable examples of a group R^2' and R^3' which is convertible to R^2 and R^3 , include alkoxy carbonyl and benzyl or *para*-methoxybenzyl which are converted to R^2 and R^3 is hydrogen using conventional conditions.

R^1 halo and R^4 halo may be introduced by selective halogenation of the ring P or the benzene ring of J ring respectively using conventional conditions.

It should be appreciated that it may be necessary to protect any hydrogen variables which are not required to be interconverted. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

It should be appreciated that it is preferred that groups R^1 to R^4 are introduced before coupling compounds of formula (II) and (III).

Compounds of formula (II) in which A is NHR^2' are known compounds or can be prepared analogously to known compounds, see, for example, WO 92/05170.

Compounds of formula (II) in which A is $-N=C=O$ may be prepared by treating a compound of formula (II) in which :

i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.

ii) A is acyl azide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions (ref L.S. Trifonov *et al*, *Helv. Chim. Acta* 1987 70 262).

iii) A is $CONH_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (II) in which A is $NR^2'COL$ may be prepared by reacting a compound of formula (II) in which A is NHR^2' with phosgene or a phosgene equivalent in an inert solvent, at low temperature, if necessary in the presence of one equivalent of a base such as triethylamine.

Compounds of formula (III) may be prepared according to known methods or analogous to known methods. For example compounds of formula (III) where B is NHR^3' where R^3' is hydrogen may be prepared by conventional reduction of the corresponding 5-nitro compounds such as those outlined in description 2 to 6.

Compounds of formula (II) in which A is halogen and R^4' is hydrogen are commercially available.

Compounds of formula (III) in which B is -N=C=O, NHR^{3'}, NR^{3'}COL and NR^{3'}CONHR^{2'} can be prepared using procedures analogous to those outlined for compounds of formula (II) above.

Examples of phosgene equivalents include triphosgene, carbonyldiimidazole, 5 phenyl chloroformate and phenyl chlorothioformate.

Pharmaceutically acceptable salts can be prepared conventionally by reaction with the appropriate acid or acid derivative. N-oxides and S-oxides can be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

Certain intermediates of formula (III) form a further aspect of the invention.

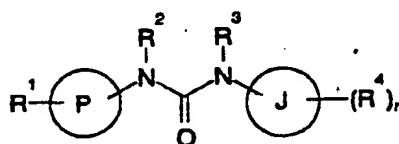
10 Compounds of formula (I) and their pharmaceutically acceptable salts have 5HT_{2C} receptor antagonist activity and are believed to be of potential use in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse, schizophrenia and/or disorders associated with spinal trauma and/or head injuries.

15 Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse, schizophrenia and/or disorders associated with spinal trauma and/or head injuries.

20 The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, the invention provides the use of a compound of formula (IA) or a salt thereof:

25



(IA)

30 wherein:

P is a quinoline, isoquinoline, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

J is a ring system selected from quinoline, tetrahydroquinoline, indoline, indazole, benzothiophene, indene, indane, benzothiazole or benzofuran;

35 R¹ is hydrogen, C₁₋₆ alkyl, halogen, NR⁵R⁶ or OR⁷, where R⁵, R⁶ and R⁷ are

independently hydrogen or C₁₋₆ alkyl; and
R² and R³ are independently hydrogen or C₁₋₆ alkyl.
R⁴ is C₁₋₆ alkyl, OR⁸ or halogen, where R⁸ is hydrogen or C₁₋₆ alkyl; and
n is 1 or 2 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament

5 for the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse, schizophrenia and/or also disorders associated with spinal trauma and/or head injuries, in particular the treatment or prophylaxis of anxiety and depression.

10 The invention further provides a method of treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse, schizophrenia and/or disorders associated with spinal trauma and/or head injuries, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a

15 compound of formula (IA) or a pharmaceutically acceptable salt thereof.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders,

20 injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

25 Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

30 Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

35 For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after

filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile 5 vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders 10 will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a 15 number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

Description 1**5-Nitrobenzo[b]thiophene (D1)**

5 Ethyl 5-nitrobenzo[b]thiophenecarboxylate was prepared and hydrolysed to the corresponding acid as described by S. Rossi and R. Trave (II Farmaco - Ed. Sci., 1960, 15, 396). 5-Nitrobenzo[b]thiophenecarboxylic acid (4.32 g, 19.4 mmol) was heated with copper powder (1.2 g, activated by heating for several hours at 160°C *in vacuo*) in quinoline (25 ml) at 180-190°C for 2h. After cooling, the mixture was diluted with ether and washed thoroughly with 5N hydrochloric acid. The organic phase was dried and evaporated, and the crude product was recrystallised from ether to give the title compound (3.24 g, 77%), m.p. 142-145°C.

10 15 NMR (CDCl₃) δ: 7.52 (1H, d, J 6), 7.68 (1H, d, J 6), 8.00 (1H, d, J 8), 8.22 (1H, dd, J 8, 2), 8.74 (1H, d, J 2).

Description 2**5-Aminobenzo[b]thiophene (D2)**

20 Hydrazine hydrate (85% aqueous solution, 2 ml) was added portionwise to a suspension of Raney nickel (0.25 g) and 5-nitrobenzo[b]thiophene (D1) (1.79 g, 10 mmol) in ethanol (50 ml), with shaking. After 0.5h at room temperature a further portion (0.5 ml) of hydrazine solution was added and the mixture was heated under reflux for 0.5h. The cooled reaction mixture was filtered through kieselguhr and the filtrate was evaporated *in vacuo*. The residue was recrystallised from ether/petrol to give the title compound (1.18 g, 79%), m.p. 70-72°C.

25 NMR (CDCl₃) δ: 6.79 (1H, dd, J 8, 2), 7.10 (1H, d, J 2), 7.15 (1H, d, J 6), 7.39 (1H, d J 6), 7.63 (1H, d, J 8).

30

Description 3**5-Aminoindene (D3)**

35 5-Nitroindene was prepared by the method of P. Wan *et al.* (J. Org. Chem., 1989, 54, 1354), but with chlorobenzene replacing toluene for the final dehydration step. A mixture of 5-nitroindene (0.76 g, 4.7 mmol), anhydrous tin (II) chloride (5.4 g) and ethanol (100 ml) was heated under reflux for 3.5 h, then poured onto ice and extracted with dichloromethane/THF. The aqueous phase was basified with dilute ammonia and extracted

again with dichloromethane/THF. The organic extract was filtered through kieselguhr, dried and evaporated, and the residue was dissolved in dichloromethane, filtered again and evaporated to give the title compound (0.44 g, 71%) as a gummy solid.

5 NMR (CDCl₃) δ: 3.30 (2H, s), 3.52 (2H, broad s), 6.55 (2H, m), 6.78 (2H, m), 7.24 (1H, d, J 7).

Description 4

1,1-Dimethyl-5-aminoindene (D4)

10 1,1-Dimethyl-5-nitroindene was prepared by the method of Wan *et al.*, as modified in Description 3, using 3,3-dimethyl-6-nitro-1-indanone (J. G. Smith and M. P. and M. P. Massicotte, Org. Prep. Int., 1978, 10, 123) as starting material. A mixture of 1,1-dimethyl-5-nitroindene (0.47 g, 2.5 mmol) tin (II) chloride (2.87 g) and ethanol (50 ml) was heated under reflux overnight. The mixture was poured onto ice and extracted with dichloromethane. The aqueous phase was then basified with dilute ammonia and extracted with dichloromethane/THF. The organic extract was washed with water, dried and evaporated to give the title compound (0.24 g, 61%) as an oil.

20 NMR (CDCl₃) δ: 1.28 (6H, s), 6.35 (1H, d, J 6), 6.52 (1H, d, J 6), 6.55 (1H, dd, J 8,2), 6.68 (1H, d, J 2), 7.09 (1H, d, J 8).

Description 5

5-Aminobenzothiazole (D5)

25 5-Nitrobenzothiazole was prepared by the method of I. Spieler and B. Prijs (Helv. Chim. Acta., 1950, 33, 1429). To a suspension of 5-nitrobenzothiazole (0.13 g, 0.72 mmol) and Raney nickel (0.025 g) in ethanol (5 ml) was added hydrazine hydrate (0.25 ml) in small portions. The mixture was then heated under reflux for 75 mins, cooled, filtered through 30 Kieselguhr and evaporated. The residue was chromatographed on silica gel (7 g) eluted with 2% methanol/dichloromethane, to give the title compound (27 mg, 25%).

NMR (CDCl₃) δ: 3.9 (2H, broad), 6.88 (1H, d, J 8), 7.41 (1H, s), 7.71 (1H, d, J 8), 8.92 (1H, s).

Description 6**5-Aminobenzofuran (D6)**

5 5-Nitobenzofuran was prepared from 5-nitro-2-benzofurancarboxylic acid by the method of H. Erlenmeyer *et al.* (Helv. Chim. Acta, 1948, 21, 75). The nitrobenzofuran (0.24 g, 1.47 mmol) was reduced with Raney nickel (0.04 g) and hydrazine hydrate (85% aq. solution, 0.4 ml) in ethanol (10 ml) according to the procedure of Description 2. Further hydrazine hydrate and Raney nickel were added and reflux continued as required to obtain complete reaction. The initial crude product was taken up in dichloromethane, filtered and evaporated to give the title compound (0.16 g, 82%) as a dark, rather unstable oil.

10 NMR (CDCl₃) δ: 3.3 (2H, broad), 6.61 (1H, d, J 2), 6.68 (1H, d, J 8), 6.85 (1H, s), 7.32 (1H, d, J 8), 7.55 (1H, d, J 2).

15

Description 7**1-Methyl-5-nitroindoline (D7)**

20 To a stirred suspension of sodium hydride (0.35g, 12.15 mmol) in dimethylformamide (5 ml) at 0°C, under nitrogen, was added 5-nitroindoline (2g, 12.19 mmol) in dimethylformamide. After stirring for 0.5h, iodomethane (0.8 ml; 12.9 mmol) in dimethylformamide (10 ml) was added, and stirring was continued for 3h. The reaction mixture was then quenched with water, and poured onto excess water with stirring. Filtration afforded the title compound (2.18g, 99%).

25

NMR (CDCl₃) δ: 2.91 (3H, s), 6.27 (1H, d), 7.89 (1H, m), 8.09 (1H, dd).

30

Description 8**5-Amino-1-methylindoline (D8)**

35 A mixture of the nitroindoline (D7, 1.5g, 8.4 mmol) and 5% palladium on charcoal in ethanol (70 ml) was hydrogenated at 60 p.s.i. (4.14x10⁵ Pa) at room temperature for 2h. Removal of the catalyst by filtration followed by evaporation of the solvent gave the title compound (1.27g, 98%).

35

NMR (CDCl₃) δ: 2.67 (3H, s), 6.38 (1H, d), 6.5 (1H, d), 6.59 (1H, s).

Description 9**3-Pyridyl Isocyanate (D9)**

The title compound was prepared using a procedure similar to that described by L.S.

5 Trifonov *et al.*, *Helv. Chim. Acta*, 1987, **70**, 262.

Description 10**6-Trifluoroacetamidoquinoline (D10)**

10 To a solution of 6-aminoquinoline (9.9g, 69 mmol) in chloroform (200 ml) was added triethylamine (11 ml, 79 mmol) followed by trifluoroacetic anhydride (11 ml, 79 mmol) dropwise with stirring. The mixture was stirred at ambient temperature for 2 hrs and eventually set solid. The residue was partitioned between 5% methanol/chloroform (1000 ml) and water (500 ml). The organic layer was separated and dried (Na_2SO_4), filtered and evaporated to dryness. This gave the title compound (16.5 g, 100%) as a gum.

15

Description 11**6-Trifluoroacetamido-1,2,3,4-tetrahydroquinoline (D11)**

20

Nickel (I) chloride hexahydrate (3.3 g, 14 mmol) was added to a solution of 6-trifluoroacetamidoquinoline (D9) (16.5 g, 69 mmol) in methanol (250 ml) at ambient temperature with stirring. Sodium borohydride (13.4 g, 350 mmol) was then added portionwise over 20 mins resulting in a large evolution of gas. The mixture was stirred for a further 1½ hrs then concentrated *in vacuo*. The residue was treated with 5N hydrochloric acid (500 ml) and left to stand for 20 mins. The mixture was basified with 40% sodium hydroxide and extracted with dichloromethane chloride (2 x 400 ml). The organic layer was separated and dried (Na_2SO_4), filtered and evaporated to dryness. Flash chromatography on TLC silica gel eluting with 0-4% methanol/dichloromethane gave the title compound (6.5g, 39%).

30

NMR (CDCl_3) δ : 1.95 (2H, t, J 8), 2.75 (2H, t, J 8), 3.31 (2H, t, J 8), 6.44 (1H, d, J 11), 7.08 (1H, d, J 12), 7.15 (1H, s), 7.60-7.78 (1H, br s).

35

Description 12**1-Methyl-6-trifluoroacetamido-1,2,3,4-tetrahydroquinoline (D12)**

6-Trifluoroacetamido-1,2,3,4-tetrahydroquinoline (D11) (1.29g, 5.3 mmol) and 40% aqueous formaldehyde solution (4.0 ml, 53 mmol) was hydrogenated at atmospheric

pressure and ambient temperature in ethanol (80 ml) over 10% palladium/charcoal catalyst (0.5g) for 20 hrs. The mixture was filtered through kieselguhr and the filtrate evaporated to dryness. Flash chromatography of the residue on TLC silica gel eluting with 0-2% methanol/dichloromethane gave the title compound (D12) (1.21g, 89%) as an oil.

5

NMR (CDCl₃) δ : 1.91-2.03 (2H, m), 2.75 (2H, t, J 7), 2.89 (3H, s), 3.22 (2H, t, J 7), 6.51 (1H, d, J 10), 7.14-7.21 (2H, m), 7.60-7.72 (1H, br s)

Description 13
10 **6-Amino-1-methyl-1,2,3,4-tetrahydroquinoline (D13)**

1-Methyl-6-trifluoroacetamido-1,2,3,4-tetrahydroquinoline (D12) (1.21g, 4.7 mmol) in ethanol (50 ml) was heated under reflux with 10% aqueous sodium hydroxide solution (4 ml, 9.4 mmol) for 4 hrs. The mixture was evaporated to dryness and the residue 15 partitioned between water and dichloromethane. The organics were separated and dried (Na₂SO₄), filtered and evaporated to dryness to give the title compound (D13) (0.74g, 97%) as an oil.

20 NMR (CDCl₃) δ : 1.91-2.03 (2H, m), 2.72 (2H, t, J 7), 2.80 (3H, s), 3.10 (2H, t, J 7), 3.20-3.32 (2H, br s), 6.40-6.52 (3H, m).

Example 1
N'-5-(Benzo[b]thienyl)-N'-(3-pyridyl)urea

25 A suspension of 1,1'-carbonyldiimidazole (1.295 g, 8 mmol) in dichloromethane (40 ml) was cooled to 0°C, and a solution of aminobenzothiophene (D2) (1.12 g, 7.5 mmol) in dichloromethane (40 ml) was added. The mixture was stirred at 0.°C for 15 min, then solvent was removed *in vacuo* and replaced by dimethylformamide (30 ml). 3-aminopyridine (0.705 g, 7.5 mmol) was added in dimethylformamide (10 ml) and the 30 mixture was heated at approx. 120°C for 1h. After cooling the mixture was poured into water and the precipitate was filtered off, washed with water and dried. The crude product was recrystallised from dimethylsulphoxide/water in two crops, the second crop being desired product. This material was recrystallised again in the same manner to give the title compound (1.03 g, 51%), m.p. 217°C (decomp.).

35

NMR (D6-DMSO) δ: 7.34 (1H, m), 7.38 (1H, dd, J 10,2), 7.62 (1H, d, J 6), 7.74 (1H, d, J 6), 7.90 (1H, d, J 10), 7.98 (1H, d, J8), 8.13 (1H, d, J 2), 8.21 (1H, broad s), 8.63 (1H, broad s), 8.91 (2H, d, J 8).

Found: C, 62.47; H, 4.13; N, 15.45%
 $C_{14}H_{11}N_3OS$ requires C, 62.43; H, 4.12; N, 15.60%
Found: M+ 269 $C_{14}H_{11}N_3OS$ requires 269.

5 **Example 2**

N-(5-Indenyl)-N'-(3-pyridyl) urea

A solution of nicotinoyl azide (0.59 g, 4 mmol) in toluene (10 ml) was heated under reflux for 2h, then cooled and a solution of aminoindene (D3) (0.44 g, 3.36 mmol) in dichloromethane (10 ml) was added. The mixture was stirred overnight at room temperature. Addition of a little petrol (bp. 60-80°C) caused formation of a precipitate, which was filtered off and washed with petrol. The crude product was chromatographed on silica gel (50 g) eluted with 5% methanol/dichloromethane. Eluted product was recrystallised from dichloromethane/petrol to give pure title compound E2 (0.35 g, 41.5%),
15 m.p. 161-163°C.

NMR (D6-DMSO) δ : 3.37 (2H, s), 6.73 (1H, d, J 6), 6.92 (1H, d, J 6), 7.20 (1H, d, J 7),
7.32 (1H, m), 7.39 (1H, d, J 7), 7.61 (1H, s), 7.69 (1H, d, J 7), 8.19 (1H, d, J 5), 8.61 (1H, s), 8.78 (1H, s), 8.84 (1H, s).

20

Found: M+251 $C_{15}H_{13}N_3O$ requires 251.

Example 3

N-(1,1-Dimethyl-5-indenyl)-N'-(3-pyridyl) urea

25

A solution of nicotinoyl azide (0.25 g, 1.7 mmol) in toluene (5 ml) was heated under reflux for 2h, then cooled and a solution of aminoindene (D4) (0.24 g, 1.5 mmol) in dichloromethane (5 ml) was added. The mixture was stirred overnight at room temperature, then dichloromethane, was removed under vacuum and petrol was added, causing the product to separate as an oil. Solvent was removed and the oil was triturated with ether. Evaporation *in vacuo* gave a solid foam. The crude product was chromatographed on silica gel (12.5 g) eluted with 2 - 4% methanol/dichloromethane. Eluted product was recrystallised from dichloromethane/petrol to give the title compound (0.18 g, 43%), mp. 150-155°C.

35

NMR (CDCl₃) δ : 1.24 (6H, s), 6.35 (1H, d, J 6), 6.49 (1H, d, J 6), 7.06 (1H, d, J 8),
7.18 (2H, m), 7.29 (1H, s), 7.80 (1H, s), 8.02 (1H, d, J 8) 8.16 (1H, s), 8.18 (1H, d, J 5),
8.34 (1H, s).

Found: C, 72.41; H, 6.28; N, 14.91%
 $C_{17}H_{17}N_3O$ requires C, 73.10; H, 6.13; N, 15.04%
Found: $M^+ 279$ $C_{17}H_{17}N_3O$ requires 279.

5

Example 4
N-(5-Benzothiazolyl)-N'-(3-pyridyl) urea

A solution of nicotinoyl azide (29 mg, 0.2 mmol) in toluene (1 ml) was heated under reflux
10 for 2h, then cooled and a solution of aminobenzo-thiazole (D5) (27 mg, 0.18 mmol) in dichloromethane (1 ml) was added. The mixture was stirred at room temperature for 1h, then the precipitated product was filtered off, washed with petrol and dried *in vacuo* to give the title compound (31 mg, 64%), mp 206-211°C.
15 NMR (D6-DMSO) δ: 7.35 (1H, m), 7.50 (1H, d, J 8), 7.99 (1H, d, J 8), 8.08 (1H, d, J 8), 8.21 (1H, d, J 5), 8.35 (1H, s), 8.64 (1H, s), 8.98 (1H, s), 9.10 (1H, s), 9.49 (1H, s).

HPLC analysis indicates 89.7% purity.

Found: $M^+ 270$ $C_{13}H_{10}N_4OS$ requires 270.

20

Example 5
N-(5-Benzofuryl)-N'-(3-pyridyl) urea

A solution of nicotinoyl azide (0.19 g, 1.28 mmol) in toluene (5 ml) was heated at 100°C
25 for 2H, then cooled and a solution of 5-aminobenzofuran (D6) (0.16 g, 1.2 mmol) in dichloromethane (5 ml) was added. The mixture was stirred overnight at room temperature and the precipitated product was filtered off, washed with petrol and dried. The crude product was recrystallised from dichloromethane/methanol to give the title compound (0.17 g, 56%), mp. 159-162°C.
30 NMR (D6-DMSO) δ: 6.94 (1H, d, J 2), 7.30 (2H, m), 7.52 (1H, d, J 8), 7.83 (1H, d, J 2), 7.95 (1H, s), 7.97 (1H, d, J 2), 8.20 (1H, s), 8.62 (1H, s), 8.86 (2H, d, J 5).

Found: C, 65.78; H, 4.41; N, 16.60%; $C_{14}H_{11}N_3O_2$ requires C, 66.40; H, 4.38; N, 16.59%.
35 Found: $M^+ 253$; $C_{14}H_{11}N_3O_2$ requires 253.

Example 6**N-(1-Methyl-5-indinyl)-N'-(3-pyridyl)urea dihydrochloride**

To a solution of the aminoindoline (D8) (1.27g; 8.58 mmol) in dry dichloromethane (20 ml) at 0°C was added triethylamine (1.3 ml). After stirring for 0.5h, a 12.5% solution of phosgene in toluene (10.2 ml, 11.79 mmol) was added and stirring continued for 0.5h. Triethylamine (2.63 ml) was then added and after another 0.5h, a solution of 3-aminopyridine (0.8g; 8.5 mmol) in dry dichloromethane (10 ml) added and the reaction mixture left for 2h at room temperature. Several drops of aqueous sodium hydroxide in water (5 ml) was added to the reaction mixture which was vigorously stirred for 0.5h. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulphate and evaporated to dryness. Chromatography on silica using dichloromethane as eluant afforded the title compound (1.39g, 60%) which was converted to the dihydrochloride salt using 15 hydrogen chloride in ether/ethanol. mp 252°C.

NMR (D6 DMSO) δ: 3.21 (3H, s), 3.32 (2H, m), 4 (2H, m), 7.42 (4H, m), 7.9 (1H, m), 8.35 (2H, m), 9.08 (1H, s).

m/z (E.I.): 268 (M⁺)

20

Example 7**N-5-(Benzo[b]thienyl)-N'-(2-methyl-4-quinolyl) urea**

The title compound was prepared from 2-methyl-4-aminoquinoline, 1,1'-carbonyl diimidazole and 5-aminobenzo[b]thiophene (D2) in 46% yield, m.p. 110 - 115°C.

NMR (DMSO) δ: 2.61 (3H, s), 7.39 - 7.48 (2H, m), 7.58 - 7.63 (1H, t, J = 6), 7.7 - 7.8 (2H, m), 7.89 - 7.98 (2H, m), 8.17 - 8.21 (3H, m), 9.22 (1H, s), 9.45 (1H, s).

30

Example 8**N-(3-Pyridyl)-N'-(6-quinoliny) urea dihydrochloride**

A solution of 6-aminoquinoline (0.5g, 0.30 mM) in dichloromethane (4.0 ml) was added dropwise to a solution of 3-pyridyl isocyanate (D9), prepared from 3-pyridinecarbonyl azide (0.55g, 0.37 mM) in toluene (5.0 ml), at room temperature. The reaction mixture was stirred for 18h, then cooled, and the precipitate collected by filtration to give the crude product (0.91g; 99%). This was dissolved in hot ethanol and ethereal hydrogen chloride added to afford the title compound as its dihydrochloride salt (1.0g, 85%) m.p. 215-220°C.

NMR (d₆-DMSO) δ: 7.01 (1H, t, J=6Hz), 7.20-7.38 (2H, m), 7.41-7.54 (2H, m), 7.88-8.03 (1H, m), 8.28-8.39 (1H, m), 8.45-8.60 (1H, m), 9.06-9.16 (1H, m), 9.71 (1H, s) 10.55 (1H, s).

5

Found: C, 51.67; H 4.07; N, 16.02%
 $C_{15}H_{12}N_4O \cdot 2HCl \cdot 2/3 H_2O$ requires: C, 51.60; H, 3.85; N, 16.04%

Example 9

10 **N-(3-Pyridyl)-N¹-(3-quinoliny) urea dihydrochloride**

The title compound was prepared in 82% yield from 3-aminoquinoline and 3-pyridyl isocyanate (D9) using a procedure similar to that in Example 8. m.p. 180-3°C.

15 NMR (d₆-DMSO) δ: 7.60-7.97 (2H, m), 7.98-8.10 (1H, m), 8.10-8.28 (2H, m), 8.30-8.68 (2H, m), 8.75-8.96 (1H, m), 9.05-9.33 (2H, m), 10.70 (1H, s), 11.00 (1H, s).
 Found: M⁺ 264.1011 $C_{15}H_{12}N_4O$ requires: 264.0991

Example 10

20 **N-(2-Methyl-4-quinoliny)-N¹-(3-pyridyl) urea dihydrochloride**

The title compound was prepared in 46% yield from 4-amino-2-methylquinoline and 3-pyridyl isocyanate (D9) using a procedure similar to that described in example 8, except that chloroform was substituted for dichloromethane and the whole was heated under reflux for 1h instead of being stirred at room temperature.

25 NMR (d₆-DMSO) δ: 2.89 (3H, s), 7.78-7.79 (2H, m), 8.08 (1H, t, J=8 Hz), 8.16-8.26 (1H, m), 8.27-8.39 (1H, m), 8.50-8.84 (1H, m), 9.00-9.18 (1H, m), 11.26 (1H, s), 12.20 (1H, s).
 30 Found: C, 54.62; H, 4.54; N, 15.82; Cl 19.78%
 $C_{16}H_{14}N_4O \cdot 2HCl \cdot 0.15H_2O$ requires: C, 54.31; H, 4.64; N, 15.83; Cl 20.04%

Example 11**N-(3-Pyridyl)-N'-(5-quinolinyl) urea dihydrochloride**

5 The title compound was prepared in 67% yield from 5-aminoquinoline and 3-pyridyl isocyanate (D9) using a procedure similar to that in Example 8. m.p. 251-20.

NMR (d_6 -DMSO) δ : 7.85-8.10 (4H, m), 8.27-8.48 (2H, m) 8.49-8.65 (1H, m) 9.07-9.30 (2H, m), 9.39-9.58 (1H, m), 10.40 (1H, s), 11.30 (1H, s).

10 Found: C 54.17; H, 4.15; N, 16.48; Cl 20.98%

$C_{15}H_{12}N_4O.2HCl$ requires: C, 53.43; H, 4.18; N, 16.61; Cl, 21.03%

Example 12**N-(3-Pyridyl)-N'-(8-quinolinyl) urea dihydrochloride**

The title compound was prepared in 81% yield from 8-aminoquinoline and 3-pyridyl isocyanate (D9) using a procedure similar to that in Example 8. m.p. 200-20°C.

20 NMR (d_6 -DMSO) δ : 7.50-7.83 (3H, m), 7.94-8.17 (1H, m), 8.30-8.75 (4H, m), 8.87-9.08 (1H, m), 9.20-9.38 (1H, m), 10.02 (1H, s), 11.35 (1H, s).

Found: C, 53.37; H, 4.23; N 16.57; 20.80%

$C_{15}H_{12}N_4O.2HCl$ requires: C, 53.43; H, 4.18; N, 16.61; Cl, 21.03%

25 **Example 13**
N-(5-Indanyl)-N'-(3-pyridyl) urea

The title compound was prepared in 56% yield from 5-aminoindane and nicotinoyl azide using a procedure similar to that for Example 2, m.p. 197-199°C.

NMR (D_6 -DMSO) δ : 2.00 (2H, m), 2.61 (4H, m), 7.15 (2H, m), 7.30 (1H, m), 7.39 (1H, s), 7.94 (1H, d, J 8), 8.18 (1H, d, J 8), 8.61 (1H, s), 8.65 (1H, s), 8.78 (1H, s)

35 Found: C, 71.33; H, 6.17; N, 16.84%

$C_{15}H_{15}N_3O$ requires C, 71.13; H, 5.97; N, 16.59%

Found: M^+ 253 $C_{15}N_{15}N_3O$ requires 253

Example 14**N-(3-Pyridyl)-N'-(6-(1-methyl-1,2,3,4-tetrahydro)quinolinyl)urea**

5 The title compound was prepared as in the method of Example 2 from 3-nicotinoyl azide and 6-amino-1-methyl-1,2,3,4-tetrahydroquinoline (D13). Recrystallisation of the solid obtained from methanol/ethyl acetate gave the title compound (0.85g, 66%) as a white crystalline solid m.p. 174-6° C.

10 NMR (DMSO-d₆) δ: 1.82-1.93 (2H, m), 2.68 (2H, t, J 7), 2.79 (3H, s), 3.11 (2H, t, J 7), 6.51 (1H, d, J 10), 6.99-7.08 (2H, m), 7.23-7.31 (1H, m), 7.89-8.07 (1H, m), 8.12-8.17 (1H, m), 8.31 (1H, s), 8.55 (1H, s), 8.69 (1H, s)

Found: C, 67.69; H, 6.44; N, 19.71%

C₁₆H₁₈N₄O requires C, 68.06; H, 6.43; N, 19.84%

15

Example 15**N-(1-methyl-5-indazolyl)-N'-(3-pyridyl)urea**

20 The title compound was prepared in 93% yield from 1-methyl-5-aminoindazole and nicotinoyl azide using a procedure similar to that for Example 2, m.p. 200° C.

NMR (D₆-DMSO) δ: 4.01 (3H, s), 7.26-7.40 (2H, m), 7.57 (1H, d, J 8), 7.88-8.00 (3H, m), 8.18 (1H, d, J 4), 8.61 (1H, d, J 3), 8.80 (1H, s), 8.85 (1H, s)

25 Found: C, 62.84; H, 4.89; N, 26.06%

C₁₄H₁₃N₅O requires C, 62.91; H, 4.90; N, 26.20%Found: M⁺ 267 C₁₄H₁₃N₅O requires 267**Example 16****N-(3-Methyl-5-benzo[b]thienyl)-N'-(3-pyridyl)urea**

A solution of nicotinoyl azide (1.06g, 7.2mmol) in dry toluene (40ml) was heated under reflux for 2h, then cooled. A solution of 5-amino-3-methylbenzo[b]thiophene (N.B. Chapman, K.Clarke and S.N. Sawhney, *J.Chem.Soc* (C), 1968, 518; 1.18g, 7.2 mmol) in dry dichloromethane was added and the mixture was stirred overnight at room temperature. The precipitate was filtered off, washed with petrol and recrystallised from

dichloromethane/methanol/petrol, to give the title compound (1.64g, 80%),
mp. 202.5-203.5°C

Found: C, 63.18; H, 4.75; N, 14.78%
5 C₁₅H₁₃N₃OS requires: C, 63.58; H, 4.62; N, 14.83%

NMR (d₆-DMSO) δ: 2.32 (3H, s), 7.28-7.4 (3H, m), 7.85 (1H, d, J=8), 7.97 (1H, d, J=8),
7.99 (1H, s), 8.18 (1H, d, J=5), 8.61 (1H, d, J=2), 8.88 (1H, s), 8.95 (1H, s).

10 **Example 17**
N-(2-Methyl-5-benzo[b]thienyl)-N'-(3-pyridyl)urea

The title compound was prepared by a similar method to that described in Example 16,
starting from nicotinoyl azide (0.105g, 0.68 mmol) and 5-amino-2-methyl
15 benzo[b]thiophene (0.11g, 0.67mmol). The precipitate was filtered off, washed with petrol
and dried *in vacuo* to give the title compound (0.15g, 79%), mp 178-182°C.

Found: C, 63.24; H, 4.73; N, 14.97%
C₁₅H₁₃N₃OS requires C, 63.58; H, 4.62; N, 14.83%

20 NMR (d₆-DMSO) δ: 2.54 (3H, s), 7.08 (1H, s), 7.25-7.35 (2H, m), 7.74 (1H, d, J=8),
7.93-7.98 (2H, m), 8.19 (1H, d, J=5), 8.61 (1H, s), 8.88 (2H, s).

25 **Example 18**
N-(4-Methyl-5-benzo[b]thienyl)-N'-(3-pyridyl)urea

This compound was prepared by the method of Example 17, starting from nicotinoyl azide
(95mg, 0.65mmol) and 5-amino-4-methylbenzo[b]thiophene (0.105g, 0.64 mmol). Yield
0.15g, 83%, mp ~200°C (phase change), ~300°C (sublimation).

30 Found: C, 63.37; H, 4.66; N, 14.97%
C₁₅H₁₃N₃OS requires C, 63.58; H, 4.62; N, 14.83%

35 NMR (d₆-DMSO) δ: 3.37 (3H, s), 7.32 (1H, dd, J=8,5), 7.54 (1H, d, J=6), 7.65 (1H, d,
J=8), 7.76 (1H, d, J=6), 7.79 (1H, d, J=8), 7.98 (1H, dm, J=8), 8.18 (1H, d, J=5), 8.28
(1H, s), 8.62 (1H, d, J=2), 9.11 (1H, s)

Example 19**N-(5-Benzo[b]thienyl)-N'-(3-methyl-5-isoxazolyl)urea**

To a solution of 1,1'-carbonyldiimidazole (0.81g, 5mmol) in dry dichloromethane (25ml) at 5 0°C was added a solution of 5-amino-3-methylisoxazole (0.44g, 4.5 mmol) in dry chloromethane (25ml). The mixture was stirred for 1h at 0°C. Solvent was then evaporated *in vacuo* and replaced by dry dimethylformamide (25ml). 5-Aminobenzo[b] thiophene (0.67g, 4.5mmol) in dimethylformamide (5ml) was added and the mixture was heated at 120°C for 1h. After cooling, the mixture was poured into water and the 10 precipitate was filtered off, washed with water and dried. The crude product was extracted with ethanol (in a Soxhlet apparatus) and the cooled ethanolic extract was filtered and evaporated. The residue was chromatographed on silica gel eluted with 5% methanol/dichloromethane and the first-eluted material was recrystallised from dichloromethane/petrol to give the title compound (0.11g, 9%), mp >178°C (decomp.)

15

Found: C, 57.41; H, 4.21; N, 14.87%

 $C_{13}H_{11}N_3O_2S$ requires C, 57.13; H, 4.06; N, 15.37%

20 NMR (d_6 - DMSO) δ : 2.17 (3H, s), 5.98 (1H, s), 7.37 (1H, dd, $J=8,2$), 7.43 (1H, d, $J=5$), 7.25 (1H, d, $J=5$), 7.92 (1H, d, $J=8$), 8.10 (1H, d, $J=2$), 8.95 (1H, s), 10.11 (1H, s)

Example 20**N-(5-Benzo[b]thienyl)-N'-(3-methyl-5-isothiazolyl)urea**

25 This compound was prepared by a similar method to that described in Example 19, starting from 5-amino-3-methylisothiazole hydrochloride (0.45g, 3mmol), carbonyldiimidazole (0.53g, 3.3mmol) and 5-aminobenzo[b]thiophene (0.45g, 3mmol). Triethylamine (0.42ml, 3mmol) was added to the solution of isothiazole hydrochloride before adding to the carbonyldiimidazole solution. After addition to water, the crude product was washed with 30 water, dried, and recrystallised from dichloromethane/ethanol to give the title compound (0.64g, 83%), mp. 221-224°C.

Found: C, 54.17; H, 4.00; N, 14.20%

 $C_{13}H_{11}N_3OS_2$ requires: C, 53.96; H, 3.83; N, 14.52%

35

NMR (d_6 -DMSO) δ : 2.30 (3H, s), 6.68 (1H, s), 7.39 (1H, dd, $J=8,2$), 7.43 (1H, d, $J=5$), 7.76 (1H, d, $J=5$), 7.92 (1H, d, $J=8$), 8.12 (1H, d, $J=2$), 9.22 (1H, s), 10.38 (1H, s)

Pharmacological data**[³H]-mesulergine binding to rat 5-HT_{2C} clones expressed in 293 cells in vitro**

5 Evidence from the literature suggests that 5-HT_{2C} antagonists may have a number of therapeutic indications including the treatment of anxiety, migraine, depression, feeding disorders and obsessive compulsion disorders. (Curzon and Kennett, 1990; Fozard and Gray, 1989) and Alzheimer's Disease (Lawlor, 1989, J. Arch. Gen. Psychiat. Vol. 46 p.542).

10 The affinity of test drugs for the 5-HT_{2C} binding site can be determined by assessing their ability to displace [³H]-mesulergine from 5-HT_{2C} clones expressed in 293 cells (Julius *et al.*, 1988). The method employed was similar to that of Pazos *et al.*, 1984.

15 The cells suspension (50ml) was incubated with [³H]-mesulergine (0.5nM) in Tris HCl buffer (pH 7.4) at 37°C for 30 minutes. Non-specific binding was measured in the presence of mianserin (10⁻⁶M). Ten concentrations of test drug (3 x 10⁻⁹ to 10⁻⁴M final concentration) were added in a volume of 50ml. The total assay volume was 500ml. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting. The IC₅₀ values were determined using a four parameter logistic program (DeLean 1978) and the pK_i (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where:

$$K_i = \frac{IC_{50}}{\frac{1+C}{K_d}}$$

25 K_i = inhibition constant.

30 C = concentration of [³H]-mesulergine

35 K_d = Affinity of mesulergine for 5-HT_{2C} binding sites.

Curzon, G.A. and Kennett, G.A. (1990). TIPS, Vol. 11, 181-182.

Fozard, J.R. and Gray, J.A. (1989). TIPS, Vol. 10, 307-309.

Pazos, A. *et al.* (1984). Eur. J. Pharmacol., 106, 531-538.

Julius *et al.* (1988) Science 241, 558-564

DeLean A, Munson P.J., Rodbaud D (1978) Am. J. Physiol 235, E97-E102.

Results: The compounds of examples 1 to 15 had a pK_i of greater than 6.

Reversal of mCPP-induced Hypolocomotion

Administration of m-(chlorophenyl)piperazine (mCPP) to rats induces hypolocomotion (Kennett and Curzon 1988, Luckie *et al.* 1989) as seen with the related drug 1-(m-trifluoromethylphenyl)piperazine (TFMPP) (Lucki and Frazer 1982, Kennett and Curzon 1988). This effect was blocked by the non specific 5-HT_{2C}/5-HT₂ receptor antagonists mianserin, cyproheptadine and metergoline and perhaps by mesulergine. It was not blocked by the 5-HT_{2A} receptor antagonists ketanserin and ritanserin at relevant doses (Kennett and Curzon 1991) nor by antagonists of 5-HT_{1A}, 5-HT_{1B}, 5-HT₃, α_2 adrenoceptors or dopamine D₂ receptors. The effect of mCPP is therefore considered to be mediated by 5-HT_{1C} receptors (Kennett and Curzon 1988) as confirmed by subsequent studies (Lucki *et al.*, 1989). Since mCPP causes hypolocomotion when infused into the cerebral ventricles this effect is probably centrally mediated (Kennett and Curzon 1988).

mCPP-induced hypolocomotion was measured in automated locomotion cages of dimensions 56 cm long x 16½ cm wide x 25 cm high and made of black perspex. Two photobeams traversed the width of the cages at either end at ground level. Sequential breaking of these beams allowed the measurement of cage transits.

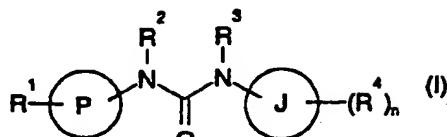
Male Sprague Dawley rats (200-250g) (Charles River) were housed in groups of six. They were given drugs orally 1h pretest and 40 mins later mCPP (7 mg/kg i.p.). After a further 20 min they were placed in individual automated cages in groups of four under red light in an adjacent room. After 10 min the test was terminated. Reversal of mCPP-induced hypolocomotion was considered as evidence of *in vivo* central 5-HT_{2C} receptor antagonist properties.

25 Kennett, G.A., Curzon, G., (1988). *Brit. J. Pharmacol.* **94**, 137-147.
Kennett G.A., Curzon, G., (1991). *Brit. J. Pharmacol.* **103**, 2016-2020.
Lucki, I., Frazer, A., (1982) *Am. Soc. Neurosci.* 8(abstr.), 101.
Lucki, I., Ward, M.R., Frazer, A., (1989). *J. Pharmacol. Exp. Therap.* **249**, 155-164.

30 **Result:** The compound of Example 1 had an ID₅₀ of 20.3 mg/kg p.o.

CLAIMS.

1. A compound of formula (I) or a salt thereof:



wherein:

P is a quinoline, isoquinoline, or a 5- or 6-membered aromatic heterocyclic ring containing
 10 up to three heteroatoms selected from nitrogen, oxygen or sulphur;

J is a ring system selected from quinoline, tetrahydroquinoline, indoline, indazole, benzothiophene, indene, indane, benzothiazole or benzofuran;

R¹ is hydrogen, C₁₋₆ alkyl, halogen, NR⁵R⁶ or OR⁷, where R⁵, R⁶ and R⁷ are independently hydrogen or C₁₋₆ alkyl; and

15 R² and R³ are independently hydrogen or C₁₋₆ alkyl.

R⁴ is C₁₋₆ alkyl, OR⁸ or halogen, where R⁸ is hydrogen or C₁₋₆ alkyl; and
 n is 1 or 2;

provided that:

- when P is other than pyridyl, J is not indoline,

20

- P and J are not both 6-methoxy quinoline, 8-hydroxy quinoline or 2-methyl quinoline,
- when J is quinoline or 2-methyl quinoline, P is not 2-thiazolyl,
- when P and J are both quinoline and R¹, R² and R³ are all hydrogen, R⁴ is not hydrogen or 6-methoxy.

25 2. A compound according to claim 1 in which P is 3-pyridyl.

3. A compound according to claim 1 or 2 in which R¹, R², and R³ are all hydrogen.

4. A compound according to claim 1 which is

30 N-5-(Benzo[b]thienyl)-N'-(3-pyridyl)urea
 N-(5-Indenyl)-N'-(3-pyridyl) urea
 N-(1,1-Dimethyl-5-indenyl)-N'-(3-pyridyl) urea
 N-(5-Benzothiazolyl)-N'-(3-pyridyl) urea
 N-(5-Benzofuryl)-N'-(3-pyridyl) urea

35 N-(1-Methyl-5-indolinyl)-N'-(3-pyridyl)urea

- N-(3-Pyridyl)-N'-(3-quinoliny) urea
- N-(3-Pyridyl)-N'-(6-quinoliny) urea
- N-(2-Methyl-4-quinoliny)-N'-(3-pyridyl) urea
- N-5-(Benzo[b]thienyl)-N'-(2-methyl-4-quinolyl) urea
- 5 N-(3-Pyridyl)-N'-(5-quinoliny) urea
- N-(3-Pyridyl)-N'-(8-quinoliny) urea
- N-(5-Indanyl)-N'-(3-pyridyl) urea
- N-(3-Pyridyl)-N'-(6-(1-methyl-1,2,3,4-tetrahydro)quinoliny)urea
- N-(1-methyl-5-indazolyl)-N'-(3-pyridyl)urea
- 10 N-(3-Methyl-5-benzo[b]thienyl)-N'-(3-pyridyl)urea
- N-(2-Methyl-5-benzo[b]thienyl)-N'-(3-pyridyl)urea
- N-(4-Methyl-5-benzo[b]thienyl)-N'-(3-pyridyl)urea
- N-(5-Benzo[b]thienyl)-N'-(3-methyl-5-isoxazolyl)urea
- N-(5-Benzo[b]thienyl)-N'-(3-methyl-5-isothiazolyl)urea
- 15 and pharmaceutically acceptable salts thereof.

5. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises:

- 20 the coupling of a compound of formula (II);



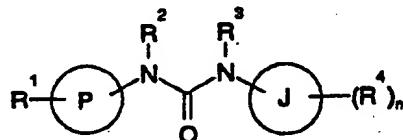
with a compound of formula (III);

- 25
- $$\text{B} - \text{J}' - \text{R}^4 \quad (\text{III})$$

wherein P is as defined in relation to formula (I), A and B contain the appropriate functional group(s) necessary to form the moiety, $-\text{NR}^2'\text{CONR}^3'$ when coupled, the variables R^1' , R^2' , R^3' and J' are R^1 , R^2 , R^3 , and J respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any R^1 , R^2 , R^3 and J , when other than R^1 , R^2 , R^3 and J respectively to R^1 , R^2 , R^3 and J , interconverting R^1 , R^2 , R^3 and J and forming a pharmaceutically acceptable salt thereof.

- 35
- 6. A compound of formula (III) as defined in claim 5.

7. A compound according to any one of claims 1 to 4 for use in therapy.
8. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier or excipient.
9. Use of a compound of formula (IA) or a pharmaceutically acceptable salt thereof.



10

(IA)

wherein:

P is a quinoline, isoquinoline, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

15 up to three heteroatoms selected from nitrogen, oxygen or sulphur;
J is a ring system selected from quinoline, tetrahydroquinoline, indoline, indazole,
imidazoline, imidazolidine, benzothiophene or benzofuran;

R^1 is hydrogen, C_{1-6} alkyl, halogen, NR^5R^6 or OR^7 , where:

20 R^2 and R^3 are independently hydrogen or C_{1-6} alkyl.

R^4 is C_{1-6} alkyl, OR⁸ or halogen, where R⁸ is hydrogen or C_{1-6} alkyl; and

n is 1 or 2 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks,

25 withdrawal from drug abuse, schizophrenia and/or also disorders associated with spinal trauma and/or head injuries

10. A method of treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse, schizophrenia and/or disorders associated with spinal trauma and/or head injuries, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

| | | | | | |
|-------------------------------------|------------|------------|------------|------------|------------|
| A. CLASSIFICATION OF SUBJECT MATTER | | | | | |
| IPC 5 | C07D409/12 | A61K31/33 | C07D213/75 | C07D417/12 | C07D401/12 |
| | C07D403/12 | C07D413/12 | | | |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO,A,92 05170 (BEECHAM GROUP PLC) 2 April 1992 * complete document * --- | 1,6,8,9 |
| P,X | WO,A,93 16694 (SMITH-KLINE BEECHAM PLC) 2 September 1993 * complete document * --- | 1,6,8,9 |
| P,X | WO,A,93 18028 (SMITH-KLINE BEECHAM PLC) 16 September 1993 * complete document * --- | 1,6,8,9 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *K* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *A* document member of the same patent family

1

Date of the actual completion of the international search

23 March 1994

Date of mailing of the international search report

- 5.04.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentam 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl.
Fax (+ 31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 93/03666

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

Information on patent family members

PCT/EP 93/03666

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|---------|------------------|
| WO-A-9205170 | 02-04-92 | AU-B- | 642041 | 07-10-93 |
| | | AU-A- | 8503891 | 15-04-92 |
| | | CA-A- | 2091246 | 14-03-92 |
| | | EP-A- | 0550507 | 14-07-93 |
| | | JP-T- | 6500551 | 20-01-94 |
| WO-A-9316694 | 02-09-93 | AU-B- | 3638393 | 13-09-93 |
| WO-A-9318028 | 16-09-93 | NONE | | |